29 Edema

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Definition

In the nonobese subject, approximately 60% of total body mass consists of water, of which two-thirds is within cells. Of the one-third confined to the extracellular space, 70% is distributed in the interstitium, 20% in the vasculature, and 10% in the central nervous system, eyes, serous cavities, and intestinal lumen. Thus a 70 kg man carries 40 kg of water, of which 24 kg is contained within cells, 11 kg within the interstitium, 3 kg in plasma, and 2 kg in other compartments.

Interstitial fluid confers a degree of turgor that the practiced examiner recognizes as normal. Although modest expansion of interstitial fluid volume may not be detected, an excess of several liters causes visible and palpable swelling. The term *edema* refers to a discernible excess of interstitial fluid. *Pitting edema* gives way on palpation, leaving persistent impressions in the skin; *brawny edema* offers resistance and leaves no impressions.

Technique

The recognition of edema is often the first step of an important and challenging clinical exercise. In most cases, optimal care of the patient with edema depends on identification of the cause (Table 29.1). Accurate diagnosis requires a complete record of the illness as experienced and transmitted by the patient, a review of several pertinent systems, a thoughtful and integrated physical examination, and a few well-selected tests.

The chronologic structure of the history is often revealing. The patient's illness may have begun with other fluid-induced symptoms, such as nocturia, paroxysmal nocturnal dyspnea, or nocturnal angina. Swelling may have come to the patient's attention because of tight-fitting shoes and rings or puffy eyes. Abrupt evolution of edema over one to a few days suggests that the underlying cause is deep venous occlusion or cellulitis, especially if the edema is accompanied by pain. A less abrupt but nevertheless rapid accumulation over several days is typical of acute glomerulonephritis. A gradual accumulation over weeks or months bespeaks an insidious systemic illness. The upright position often exacerbates idiopathic edema, and swelling during the last half of the menstrual cycle characterizes the premenstrual syndrome. Progressive accumulation of fluid through the day and resolution overnight imply that the physiologic disturbance is mild, while persistence of swelling with little diurnal variation suggests that the disturbance is more profound. Edema in a single extremity suggests local obstruction to venous or lymphatic drainage, whereas generalized edema (anasarca) is more typical of glomerulonephritis, the nephrotic syndrome, and congestive heart failure.

Because the same physiologic disturbance may cause ascites, pulmonary congestion, pleural effusion, and edema, a patient often exhibits some combination of these findings. In such cases, ascertaining whether increased abdominal girth or dyspnea appeared before or after edema may be helpful in reaching a diagnosis. Ascites usually occurs first in patients with cirrhosis or constrictive pericarditis, but it typically develops after the edema in patients with progressive right ventricular failure. Dyspnea antedates edema in left ventricular failure and primary lung disease, but may evolve simultaneously with or follow edema in acute glomerulonephritis and the nephrotic syndrome.

A careful review of systems and inquiries concerning drug ingestions and dietary habits may also aid in diagnosis. Excessive foam in the toilet bowl is indicative of albuminuria. Symptoms suggestive of thiamine deficiency, portal

Table 29.1
Causes of Peripheral Edema

I. Disorders associated with inappropriate renal sodium retention
  A. Intrinsic renal disease
    1. Acute glomerulonephritis
    2. Acute renal failure
    3. Chronic renal failure
  B. Drug-induced
    1. Nonsteroidal anti-inflammatory agents
    2. Insulin
    3. Estrogens and oral contraceptives
    4. Exogenous mineralocorticoids
  C. Refeeding edema
II. Venous occlusion and its sequelae
  A. Peripheral deep vein thrombosis
  B. Postphlebitic venous insufficiency
  C. Inferior vena cava occlusion
  D. Superior vena cava occlusion
III. Idiopathic capillary leak syndrome
IV. Disorders associated with lymphedema
  A. Milroy's disease
  B. Filariasis
  C. Neoplastic obstruction of lymphatics
  D. Surgical interruption of lymphatics
V. Disorders associated with a high cardiac output
  A. Arteriovenous fistula
  B. Beriberi
  C. Anemia
  D. Thyrotoxicosis
  E. Paget's disease
VI. Disorders in which the pathogenesis is unclear
  A. Idiopathic edema
  B. Premenstrual syndrome
  C. Toxemia of pregnancy
  D. Hypothyroidism
VII. Disorders with complex pathogenesis
  A. Congestive heart failure
  B. Nephrotic syndrome
  C. Cirrhosis

hypertension, hepatocellular insufficiency, thyrotoxicosis, and anemia are obviously germane. Nonsteroidal anti-inflammatory agents commonly cause salt retention, and many drugs can incite glomerular or tubulointerstitial nephropathies. Discontinuation of diuretics or deviation from dietary salt restriction can lead to relapses of edema irrespective of the cause.

Like the history, the physical examination can be directed initially to the edema itself. Fluid typically accumulates about the ankles if the patient has been upright, but it may be in the presacral or periorbital regions if the patient has been supine. Although grading systems provide a shorthand for describing leg edema, it is preferable to report the location and extent completely. Acute swelling typically pits with minimal pressure, whereas chronic edema usually offers more resistance. Chronic edema is often associated with cutaneous hyperpigmentation and occasionally provokes an eczematous dermatitis.

The distribution of edema provides numerous diagnostic hints. If edema is confined to one leg, consider deep vein thrombosis, postphlebitic changes, cellulitis, lymphangitis, and inguinal lymphadenopathy. If one arm is involved, consider venous and lymphatic occlusion and cellulitis, and direct special attention to the ipsilateral breast and axilla. If both arms are swollen, obstruction of the superior vena cava is the most likely cause, especially if the face is also suffused. Swelling of both legs suggests chronic venous insufficiency, cirrhosis with portal hypertension, nephrotic syndrome, acute glomerulonephritis, right ventricular failure, or constrictive pericarditis. All four extremities and the torso may be edematous in some instances of cardiac and renal disease.

Other findings can assist in reaching a diagnosis. Systemic hypertension typically complicates acute glomerulonephritis, often accompanies the nephrotic syndrome, but almost never occurs in cirrhosis. A widened pulse pressure is typical of conditions associated with a high cardiac output. Neck vein distention directs attention to high output states, glomerulonephritis, and intrinsic heart disease, but it cannot be attributed to cirrhosis. Kussmaul's sign suggests restrictive cardiomyopathy or constrictive pericarditis. If plasma oncotic pressure is not markedly reduced, the presence of pleural effusions suggests that both left and right atrial pressures are elevated. Splenomegaly speaks more for cirrhosis than for heart failure in the edematous patient with ascites. A totally normal examination suggests the diagnosis of idiopathic edema, especially if the patient is a woman in her childbearing years.

Appropriate laboratory tests are dictated by the differential diagnosis. Anemia must be sought because it can cause a high output state or exacerbate underlying myocardial disease. The serum creatinine provides a sufficient screen for advanced renal insufficiency, and the serum albumin permits a useful approximation of the plasma oncotic pressure. The urinalysis reveals proteinuria in the nephrotic syndrome, and hematuria and casts in the urinary sediment suggest glomerulonephritis. The serum bilirubin and hepatocellular enzymes provide an initial assessment of liver function. An isolated elevation of alkaline phosphatase arouses suspicion of Paget's disease. The chest x-ray helps to distinguish parenchymal lung disease from pulmonary vascular congestion and corroborates other impressions gained from physical examination. The electrocardiogram can provide confirmatory evidence of pericardial and valvular disease, coronary arteriosclerosis, and systemic and pulmonary hypertension.

Basic Science

Edema accumulates in interstitial spaces surrounding capillary beds. The movement of fluid between capillaries and the interstitium is governed by the formula:

$$J_v = k[(P_c - P_i) - (\pi_c - \pi_i)]$$

where J_v is the rate of flux across the capillary membrane, k is a constant denoting membrane permeability, P_c is capillary hydraulic pressure, P_i is interstitial hydraulic pressure, π_c is capillary oncotic pressure, and π_i is interstitial oncotic pressure. The equation indicates that capillary hydraulic pressure and interstitial oncotic pressure enhance flux out of capillaries, while capillary oncotic pressure and interstitial hydraulic pressure enhance flux into capillaries. These pressures are called *Starling forces* in honor of the physiologist who clearly articulated their relationship. Although their absolute values vary considerably at different sites in the body, the interplay among them at a given site always predisposes to net accumulation of interstitial fluid. Fortunately, lymphatic channels return this fluid to the systemic circulation as rapidly as it accumulates, thus preventing edema formation while maintaining normal intravascular volume.

The presence of edema implies that interstitial fluid volume exceeds the normal by several liters. With rare exceptions, net renal sodium retention generates this excess. At the same time, edema can accumulate only if one or more of the Starling forces is altered or lymphatic drainage is interrupted. In some conditions, the primary lesion is an imbalance of Starling forces that accelerates transudation of fluid into the interstitium; secondary depletion of intravascular volume is perceived at carotid and renal arterial baroreceptors, and sodium conservation is stimulated. In other disorders, inappropriate sodium retention is the proximal disturbance; the resulting expansion of extracellular fluid volume produces secondary alterations in Starling forces that lead to the formation of edema. In at least one edema-forming state, the nephrotic syndrome, unphysiologic sodium conservation and a reduction in oncotic pressure occur simultaneously. In the premenstrual syndrome, idiopathic edema, and hypothyroidism, the primary lesions are a matter of debate.

The mechanisms by which the kidneys retain sodium in response to hypoperfusion can be viewed as reflexes with afferent (sensor) and efferent (effector) limbs. Although sensors of intravascular volume have been described in the liver, the renal parenchyma, and the cardiac atria, the most important in human edema-forming conditions are probably the carotid baroreceptor and the juxtaglomerular apparatus. Impulses arising from the carotid baroreceptor enter the central nervous system via the ninth and tenth cranial nerves; the resulting sympathetic outflow to the kidney modulates intraglomerular hemodynamics and probably stimulates proximal tubular sodium reabsorption directly. In the kidney, hypoperfusion causes autoregulatory dilation of afferent arterioles, which stimulates renin release from specialized cells in the arteriolar wall. Renin then catalyzes the intraglomerular synthesis of angiotensin II, which selectively increases efferent arteriolar resistance. The consequent increase in filtration fraction leads to a decline in hydraulic pressure and an elevation in oncotic pressure in peritubular capillaries, thus enhancing proximal tubular sodium reabsorption while supporting glomerular filtration. Systemically, renin increases the level of circulating angi-

otensin II, which stimulates adrenal synthesis of aldosterone. This hormone enhances distal nephron sodium reabsorption in exchange for potassium and hydrogen.

The pathogenesis of edema in various disease states ranges from the straightforward to the exceedingly complex. In several conditions, inappropriate renal conservation of sodium is the initial disturbance, from which alterations in peripheral Starling forces follow. Acute glomerulonephritis and other forms of acute and chronic renal failure are in this category. Refeeding edema, which sometimes complicates administration of calories to malnourished individuals, is probably due to insulin-mediated sodium retention. The edema that can follow ingestion of nonsteroidal anti-inflammatory agents has been attributed to inhibition of renal prostaglandin synthesis. In toxemia of pregnancy, unexplained extracellular fluid volume expansion causes edema and systemic hypertension while suppressing the renin–angiotensin–aldosterone axis.

In some edema-forming states, alterations in peripheral Starling forces appear to stimulate sodium retention by depleting the intravascular volume. Such states include peripheral deep vein thrombosis and postphlebitic venous insufficiency, in which increased intracapillary hydraulic pressure augments transudation into the interstitium; states characterized by excessive capillary permeability, in which transudation is again accelerated; and diseases of lymphatics, in which interstitial fluid accumulated at a normal rate cannot be returned to the systemic circulation. Renal function in edema-forming states characterized by a high cardiac output is also physiologically appropriate. Each of the high output states is thought to result from one or many low-resistance circuits in the cardiovascular system. These circuits may pervade the microvasculature, as is probably the case in anemia, thyrotoxicosis, beriberi, and Paget's disease, or they may be large and unitary, as in traumatic arteriovenous fistula. Constant diversion of flow from the kidneys causes retention of sodium, elevation of intravascular hydraulic pressure in all capillary beds, and progressive edema.

Cardiac disorders often cause edema. Whether the inciting pathology involves the left heart only, the entire myocardium, the pericardium, or the lungs, the evolution of edema implies that mean right atrial pressure is elevated. Peripheral venous pressure must rise secondarily in order to maintain venous return against gravity, but this adjustment accelerates transudation into the peripheral interstitium. At the same time, right atrial hypertension prevents any compensatory increase in lymphatic return. Whereas peripheral edema follows dyspnea by months to years when the initial lesion is in the left heart or the lungs, the two symptoms often appear simultaneously in diffuse cardiomyopathies.

The time-honored explication of the nephrotic syndrome states that renal protein loss leads to a reduction in plasma colloid oncotic pressure; the resulting imbalance in Starling forces favors interstitial fluid accumulation at the expense of plasma volume, which the kidneys attempt to reconstitute by retaining salt and water. Unfortunately, since hypoalbuminemia persists, the renal response merely restores the imbalance that initiated edema formation, and the process continues unabated.

As attractive as this formulation is, it is at variance with several observations. First, the serum albumin concentration at which edema forms in the nephrotic syndrome varies considerably from patient to patient. Second, congenital analbuminemia may not be associated with edema at all. Third, even when proteinuria is unaccompanied by glomerular inflammation, as in nil disease, blood volume and blood pressure are often higher than when the nephrotic syndrome is in remission. Fourth, there is no correlation in nephrotic patients between serum albumin and plasma renin activity, which is ordinarily a sensitive marker for renal hypoperfusion; in some cases, despite hypoalbuminemia, plasma renin activity may be depressed. Even when reninemia is significant, angiotensin converting enzyme inhibition has little effect on blood pressure; if the renin-aldosterone axis were activated in response to volume depletion, a reduction in pressure would occur. Together, these observations suggest that the kidneys often retain sodium inappropriately in the nephrotic syndrome, even when glomerulonephritis is not evident. Although the classic formulation of pathogenesis may be accurate in some instances, it appears that hypoalbuminemia is most commonly a contributor to rather than the sole cause of edema.

The circulatory modifications that result from advanced cirrhosis are complex. Intrahepatic fibrosis raises sinusoidal pressures; hepatic lymph is consequently manufactured more rapidly than it can be returned to the circulation, and ascites accumulates. Simultaneously, the hepatic portal system and capillary beds in the skin, lungs, and intraabdominal viscera develop fistulas that divert flow from the kidneys. Acute liver inflammation, if present, draws increased hepatic arterial flow. Eventually, tense ascites causes extrinsic compression of the inferior vena cava, increasing capillary hydraulic pressure in the extremities. The resulting transudation is undoubtedly enhanced by hypoalbuminemia.

Although inappropriate salt retention may occur early in the course of cirrhosis, these combined hemodynamic sequelae deprive the kidneys of blood flow as the disease progresses, and avid sodium retention follows. The extreme result of these disturbances is the hepatorenal syndrome, in which a rising serum creatinine and virtually complete conservation of filtered sodium are associated with massive sequestration of fluid in interstitial beds and the body cavities.

Clinical Significance

Edematous extremities can be painful. They are prone to stasis-induced ulceration and infection, and occasionally eczematous dermatitis develops. When the patient is supine, mobilization of interstitial fluid from the legs leads to paroxysmal nocturnal dyspnea and nocturia. The sequelae of edema thus obligate the physician to reduce it with diuretics and, if possible, with therapies specific for underlying conditions. Skill and continued surveillance are often required to achieve this objective while maintaining adequate arterial perfusion. Occasionally, these goals are mutually incompatible.

There are at least two reasons why every case of edema must be satisfactorily explained. Some edema-forming disorders, such as constrictive pericarditis, thyrotoxicosis, and beriberi, are curable. For others, such as congestive heart failure, nephrotic syndrome, and cirrhosis, appropriate treatment greatly reduces morbidity, and it may succeed in mobilizing edema resistant to diuretics alone. In almost all cases of peripheral edema, a complete, thoughtfully integrated database permits accurate identification of the cause, and the correct diagnosis dictates appropriate therapy.

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